(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2002 (13.06.2002)

PCT

(10) International Publication Number
WO 02/45688 A2

(51) International Patent Classification[7]: A61K 9/127, 31/573

(21) International Application Number: PCT/EP01/14633

(22) International Filing Date: 7 December 2001 (07.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00204372.7 7 December 2000 (07.12.2000) EP

(71) Applicant *(for all designated States except US)*: **YAMANOUCHI EUROPE B.V.** [NL/NL]; Elisabethhof 19, NL-2353 EW Leiderdorp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **METSELAAR, Josbert, Maarten** [NL/NL]; Dept. of Pharmaceutics, Faculty of Pharmacy, Utrecht Institute of Pharmaceutical Sciences, P.O. Box 80082, NL-3508 TB Utrecht (NL). **WAUBEN, Marca, Henriette, Michaela** [NL/NL]; Dept. of Immunology, Faculty of Veterinary Medicin, e, Institute of Infectious diseases and Immunology, P.O. Box 80165, NL-3508 TB Utrecht (NL). **STORM, Gerrit** [NL/NL]; Dept. of Pharmaceutics, Faculty of Pharmacy, Utrecht Institute of Pharmaceutical Sciences, P.O. Box 80082, NL-3508 TB Utrecht (NL).

(74) Common Representative: **YAMANOUCHI EUROPE B.V.**; Dept. legal Affairs Europe, P.O. Box 108, NL-2350 AC Leiderdorp (NL).

(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TT, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/45688 A2

(54) Title: COMPOSITION FOR TREATMENT OF INFLAMMATORY DISORDERS

(57) Abstract: A pharmaceutical composition for parenteral administration, comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol, and optionally including not more than 10 mole percent of negatively charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40-200 nm and containing a water soluble corticosteroid for the site-specific treatment of inflammatory disorders, is provided.

COMPOSITION FOR TREATMENT OF INFLAMMATORY DISORDERS

The present invention relates to a pharmaceutical composition for parenteral and in particular intravenous administration, comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol (PEG) and optionally including not more than 10 mole percent of negatively charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40 – 200 nm and containing a corticosteroid for the site-specific treatment of inflammatory disorders.

BACKGROUND OF THE INVENTION

Intravenous administration of compositions based on PEG-containing liposomes for the site-specific treatment of inflamed tissues and regions is already disclosed in EP-0662820. It is well-known that long-circulating small-sized liposomes, which contain non-charged or slightly negatively charged vesicle-forming lipids, such as PEG-liposomes, after intravenous administration can circulate for many hours in a volume not larger than the general circulation and therefore, in theory, are able to deliver relatively high portions of anti-inflammatory agents via extravasation at sites of enhanced vascular permeability common to inflamed regions. Such liposomes are of particular interest in the treatment of inflammatory diseases, e.g. rheumatoid arthritis, which is a chronic autoimmune disorder, causing joint inflammation and progressive cartilage destruction. Although several types of antirheumatic drugs are available for use, the treatment of severe, persistent synovitis and acute exacerbations may require the use of several intravenous injections containing high doses of glucocorticoids. Although systemic corticosteroids can suppress the symptoms of the disease, adverse effects limit their use. In addition to this, glucocorticoids suffer from unfavourable pharmacokinetic behaviour: short plasma half-life values and a large distribution volume require high and repeated administration in order to reach a therapeutically effective concentration of the drug at the desired site of action. Intra-articular injection of steroids into the affected joints is often used to increase the (local) efficacy of the glucocorticoids and diminish the systemic adverse effects, but this way of administration is less comfortable for the patients and not feasible when multiple small joints are affected.

Also, a significant incidence of painless destruction of the joint may be associated with repeated intra-articular injections of glucocorticoids. According to EP-0662820-B preferred compounds for entrapment in PEG-containing liposomes are the steroidal anti-inflammatory compounds, such as prednisone, methylprednisolone, paramethazone, 11-fludrocortisol, triamcinolone, betamethasone and dexamethasone. The steroids listed belong to the group of steroids which are systemically administered. Example no. 12 is the only example of a glucocorticoid-containing PEG-liposome in this patent and relates to the preparation of beclomethasone dipropionate-containing PEG-liposomes. However, no in vivo data were provided. On preparing dexamethasone-containing PEG-liposomes according to the disclosure in EP-0662820 and on intravenous administration of the same in an in vivo experimental arthritis model, the present inventors noted that the beneficial effects, as taught in EP-0662820, could not be observed at all. There was no difference in pharmacokinetic profile between a suspension containing the glucocorticoid and the PEG-liposomes in which the same glucocorticoid had been encapsulated.

Since glucocorticoids often are the most effective drugs in the treatment of inflammatory disorders, there is a need to provide liposomal compositions which after parenteral administration can more efficiently deliver effective amounts of glucocorticoid at the inflamed region or tissue for enhanced and prolonged local activity.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a pharmaceutical composition for parenteral administration, comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol and optionally including not more than 10 mole percent of negatively charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40 – 200 nm and containing a water soluble corticosteroid for the site-specific treatment of inflammatory disorders.

A further object of the present invention is to provide a use of a pharmaceutical composition, comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol and optionally including not more than 10 mole percent of negatively

charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40 – 200 nm and containing a corticosteroid, for the preparation of a medicament effective in the site-specific treatment of inflamed tissues or regions after parenteral administration, characterised in that the corticosteroid is used in the medicament in a water soluble form.

DETAILED DESCRIPTION OF THE INVENTION

It has now been found that by incorporating a water soluble form of a corticosteroid in long-circulating liposomes, composed of non-charged vesicle-forming lipids, including up to 20 mole percent of amphipathic vesicle-forming lipids derivatised with polyethylene glycol (PEG) and optionally including not more than 10 mole percent of negatively charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40 – 200 nm, an increased localisation and improved retention of the corticosteroid at inflamed tissue after one single intravenous injection of a pharmaceutical composition, comprising the said liposomes, can be reached as compared with one single intravenous injection of an aqueous solution containing the same corticosteroid compound.

The long-circulation liposomes according to the present invention have a circulation half life of at least 6 hours, the circulation half life being defined as the time at which the second linear phase of the logarithmic liposomal clearance profile reaches 50% of its initial concentration, which is the extrapolated plasma concentration at t=0.

The particle size of the liposomes is an important feature, which was demonstrated by the fact that administration of a water-soluble corticosteroid, such as prednisolone disodium phosphate, in PEG-liposomes, having a mean particle diameter >500 nm, did not result in a significant decrease of paw inflammation in the rat adjuvant arthritis model.

A water soluble corticosteroid in accordance with the present invention is a compound which is soluble 1 in ≤10 (w/v), as assessed in water or water buffered at physiologic values, e.g. at pH > 6.0, at a temperature between 15 and 25°C.

Water soluble corticosteroids which can be advantageously used in accordance with the present invention are alkali metal and ammonium salts prepared from corticosteroids, having a free hydroxyl group, and organic acids, such as (C_2 – C_{12}) aliphatic saturated and unsaturated dicarbonic acids, and inorganic acids, such as phosphoric acid and sulphuric

acid. Also acid addition salts of corticosteroids can advantageously be encapsulated in the long-circulating PEG-liposomes. If more than one group in the corticosteroid molecule is available for salt formation, mono- as well as di-salts may be useful. As alkaline metal salts the potassium and sodium salts are preferred. Also other, positively or negatively charged, derivatives of corticosteroids can be used. Specific examples of water soluble corticosteroids are betamethasone sodium phosphate, desonide sodium phosphate, dexamethasone sodium phosphate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone disodium phosphate, methylprednisolone sodium succinate, prednisolone sodium phosphate, prednisolone sodium succinate, prednisolamate hydrochloride, prednisone phosphate, triamcinolone acetonide disodium phosphate and triamcinolone acetonide dipotassium phosphate.

The above-mentioned corticosteroids normally are used in systemic treatment of anti-inflammatory diseases and disorders. Since it has been proven by the present inventors that by using a water-soluble form of a corticosteroid in PEG liposomes, having a specified small mean particle diameter, effective targeting of the drug to arthritic sites - by systemic administration – occurs, the present invention can advantageously be applied to corticosteroids, which - for a variety of reasons - normally are used for topical use. Such corticosteroids include for example alclomethasone dipropionate, amcinonide, beclomethasone monopropionate, betamethasone 17-valerate, ciclomethasone, clobetasol propionate, clobetasone butyrate, deprodone propionate, desonide, desoxymethasone, dexamethasone acetate, diflucortolone valerate, diflurasone diacetate, diflucortolone, difluprednate, flumetasone pivalate, flunisolide, fluocinolone acetonide acetate, fluocinonide, fluocortolone pivalate, fluormetholone acetate, fluprednidene acetate, halcinonide, halometasone, hydrocortisone acetate, medrysone, methylprednisolone acetate, mometasone furoate, parametasone acetate, prednicarbate, prednisolone acetate, prednylidene, rimexolone, tixocortol pivalate and triamcinolone hexacetonide. Topical corticosteroids, which undergo fast, efficient clearance as soon as these drugs become available in the general circulation, are of special interest. Examples thereof are budesonide, flunisolide and fluticasone propionate. By preparing a water soluble form of the above-mentioned topical steroids and encapsulating this into PEG liposomes in accordance with the present invention it is now possible to systemically administer such corticosteroids in order to reach site-specific drug delivery, thereby avoiding adverse effects associated with

systemic treatment and overcoming problems, which are inherent to the corticosteroid, such as a fast clearance. In this respect budesonide phosphate has appeared to be a salt of great interest.

The liposomes in accordance with the present invention may be prepared according to methods used in the preparation of conventional liposomes and the PEG-liposomes, as disclosed in e.g. EP-0662820. Passive loading of the active ingredients into the liposomes by dissolving the corticosteroid in the aqueous phase is sufficient in order to reach an encapsulation as high as possible, but other methods can also be used. The lipid components used in forming the liposomes may be selected from a variety of vesicle-forming lipids, such as phospholipids, sphingolipids and sterols. Substitution (complete or partial) of these basic components by e.g. sphingomyelines and ergosterol appeared to be possible. For effective encapsulation of the water-soluble corticosteroids in the liposomes, thereby avoiding leakage of the drug from the liposomes, especially phospholipid components having saturated, rigidifying acyl chains have appeared to be useful.

The beneficial effects observed after one single injection of the water soluble corticosteroid containing PEG liposomes according to the invention are very favourable when compared with the results obtained after single, but also repeated injections of the non-encapsulated water soluble corticosteroid in different concentrations. Administration of the non-encapsulated water soluble corticosteroid was much less effective than the encapsulated corticosteroid, which can be easily understood if the total amount of free versus encapsulated corticosteroid is considered: the free corticosteroid was always by a factor of at least 5-10 less effective, even when injected on 7 consecutive days. These effects have been observed in two different animal models, viz. a rat adjuvant arthritis model and a mouse model of collagen induced arthritis. The favourable effects may be a complete and long-lasting remission of all arthritis-associated symptoms, dependent of the dose. In addition thereto, in the mouse model a reduced cartilage erosion was observed one week after treatment at the time the inflammation had returned again.

Since in Experimental Autoimmune Encephalomyelitis ultra high doses of methylprednisolone have been shown to be more efficient in induction of T cell apoptosis than the "standard" dose of 10 mg/kg used in multiple sclerosis therapy, it has been investigated whether a long-circulating liposome formulation containing prednisolone is

superior to methylprednisolone pulse therapy in induction of T cell apoptosis *in situ*. It has been observed that liposomal prednisolone phosphate given at 10 mg/kg augments T cell apoptosis *in situ* rapidly and the reduced infiltration of T cells and macrophages leads to an ameliorated disease activity of Adoptive Transfer Experimental Autoimmune Encephalomyelitis (AT-EAE). As the liposomes can extravasate and accumulate in inflamed tissue with a disrupted blood-brain-barrier, liposomal prednisolone phosphate could be a therapeutical alternative to methylprednisolone, which needs a higher dosage and would therefore cause more systemic side-effects. These findings may have implications for the treatment of inflammatory autoimmune diseases of the Central Nervous System (CNS) such as multiple sclerosis.

Surprisingly, although small, rigid PEG-containing liposomes are known to hardly release their contents, the PEG-liposomes according to the present invention were able to effectively deliver the water soluble corticosteroid at the desired site of action resulting in a complete remission of the inflammation.

The following examples further illustrate the invention.

EXAMPLES

Example 1

Preparation of prednisolone phosphate-containing PEG-liposomes

750 mg of dipalmitoyl phosphatidylcholine (DPPC) (Lipoid Ludwigshafen), 250.8 mg of cholesterol (Sigma Aldrich) and 267.6 mg of PEG-distearoylphosphatidylethanol-amine (PEG-DSPE) (Avanti Polar Lipids) were weighed and mixed in a 100 ml round-bottom flask. The lipids were dissolved in about 30 ml of ethanol. Thereafter evaporating to dryness in a Rotavapor during 1 hour under vacuum at 40°C, followed by flushing with nitrogen gas during 1 hour took place.

1200 mg of prednisolon disodium phosphate (OPG Nieuwegein) were weighed and dissolved in 12 ml of sterilised PBS. The solution was added to the dry lipid film and shaked during one hour in the presence of glass beads in order to enable complete hydration of the lipid film.

The liposomal suspension was transferred to an extruder (Avestin, maximum volume 15 ml) and extruded under pressure, using nitrogen gas, 6 times through 2 pore filters one placed on top of the other, having a pore size of 200 and 100 nm respectively, 100 and 50 nm respectively and 50 and 50 nm respectively. Subsequently the liposomal suspension was dialysed in a dialysing compartment (Slide-A-Lyzer, 10.000 MWCO) 2 times during 24 hours against 1 liter of sterilised PBS.

The mean particle size of the liposomes was determined by means of light scattering (Malvern Zeta-sizer) and was found to be 93.1 ± 1.2 nm, the polydispersity index being 0.095 ± 0.024. The encapsulation efficiency of the prednisolone phosphate was determined by means of a HPLC method and was found to be between 3 and 4%. The suspension of liposomes was stored in a nitrogen atmosphere at 4°C and found to be stable for about 2 months.

Example 2

Preparation of other water soluble corticosteroid containing PEG-liposomes

Example 1 was repeated but instead of prednisolone disodium phosphate dexamethasone disodium phosphate (OPG Nieuwegein), betamethasone disodium phosphate (Sigma-

Aldrich) or budesonide 21-phosphate (prepared by Syncom, Groningen, the Netherlands) respectively was used.

Example 3

Assessment of therapeutic efficacy in rat adjuvant arthritis model

Lewis rats were immunized subcutaneously at the tail base with heat-inactivated *Mycobacterium tuberculosis* in incomplete Freund's adjuvant. Paw inflammation started between 9 and 12 days after immunization, reached maximum severity approximately after 20 days, and then gradually resolved.

Assessment of the disease was performed by visually scoring paw inflammation severity, maximum score 4 per paw, and measuring disease-induced body weight loss. The therapeutic efficacy of liposomal prednisolone phosphate, prepared according to example 1, on these variables was compared with equal doses unencapsulated drug. Rats were treated when the average score > 6 (at day 14 or 15 after disease induction).

A complete remission of the inflammation process in 4 out of 5 rats was observed within 3 days after treatment with a single dose 10 mg/kg liposomal prednisolone phosphate (average score 0.1 ± 0.1, compared to 11.8 ± 1.9 of the PBS-treated rats). Unencapsulated prednisolone phosphate did not significantly alter the course of the disease ($p > 0.05$, Kruskall-Wallis test, non-parametric). In contrast, also 1 mg/kg liposomal prednisolone phosphate was effective ($p < 0.05$, Kruskall-Wallis, non-parametric). With respect to weight loss, only 10 mg/kg liposomal prednisolone phosphate had a significant effect ($p < 0.05$, one-way ANOVA). Within 8 days these rats regained initial weight. Other treatment groups continued suffering from progressive weight loss.

No effect of a single injection unencapsulated prednisolone phosphate was observed. Therefore it was decided to inject 10 mg/kg and 20 mg/kg daily for 7 days. Both treatment regimens reduced inflammation scores from an average of 6.5 ± 0.56 (day 14) to average values around 5.0 from day 15 until day 21 (control treatment with daily saline reached a maximum of 10.6 ± 1.3 on day 20). However, single injections of 10 mg/kg and 20 mg/kg liposomal prednisolone phosphate at day 14 resulted in disappearance of adjuvant arthritis (AA) symptoms until day 20. Control treatment with empty liposomes did not result in an

altered progression of the disease ($p > 0.05$).

The liposomal compositions of example 2 were also tested in the adjuvant arthritis model. Liposomal dexamethasone phosphate proved to be more effective than either liposomal prednisolone phosphate or liposomal betamethasone phosphate. A dose of 2 mg/kg was equally effective as 10 mg/kg liposomal prednisolone phosphate. 2 mg/kg liposomal betamethasone phosphate proved to be more effective than 2 mg/kg liposomal prednisolone phosphate, however, in contrast to 2 mg/kg liposomal dexamethasone phosphate, no complete reversal was obtained. Liposomal budesonide 21-phosphate (1 mg/kg) produced at least equally effective disease suppression as compared to liposomal dexamethasone phosphate.

Example 4

Assessment of therapeutic efficacy in AT-EAE

Adoptive Transfer Experimental Autoimmune Encephalomyelitis (AT-EAE) was induced in female Lewis rats by intravenous injection of 10^7 MBP-specific T cells.

10 mg/kg prednisolone phosphate containing liposomes, as prepared according to example 1, were applied intravenously at 42 hours and 18 hours prior to sacrifice. Another group received 50 mg/kg methylprednisolone intravenously at 18 hours and 6 hours before perfusion. Control rats received empty liposomes and/or saline at equivalent time points.

T cells or macrophages in spinal cord were detected immunohistochemically in paraffin embedded tissue and apoptosis was assesed by the TUNEL assay and by morphological criteria. Student t test for grouped data was used for statistical analysis. The rate of T cell apoptosis in spinal cord tissue was significantly augmented by liposomal prednisolone phosphate (39.4 ±6.8%, $p<0.0001$ vs. 16.1 ±4.3% in the control group, all data given as mean ±SD). Methylprednisolone as an internal control lead to a rate of 30.8 ±8.0% T cell apoptosis ($p<0.01$ vs. Controls). As a result of the increase in apoptosis T cell infiltration was clearly reduced by liposomal prednisolone phosphate (45 ±12 T cells/mm^2), which was statistically significant compared to controls (115 ±51 T cells/mm^2, $p<0.05$) as well as compared to methylprednisolone (96 ±19 T cells/mm^2, $p<0.05$). As another aspect of inflammation the macrophage infiltration was significantly reduced by liposomal prednisolone phosphate (31 ±13 macrophages/mm^2) compared to controls (78 ±37

macrophages/mm^2, $p<0.05$) and compared to methylprednisolone (66 ±25 macrophages/mm^2, $p<0.05$). Even though the Adoptive Transfer model was chosen to investigate rapid mechanisms, a therapeutical benefit from liposomal prednisolone phosphate could be observed within 42 hours, achieving a clinical score of 2.8 ±0.2 compared to controls (3.2 ±0.3, $p<0.01$), which was superior to methylprednisolone (3.2 ±0.3, $p<0.05$ vs. liposomal prednisolone phosphate).

CLAIMS

1. A pharmaceutical composition for parenteral administration, the composition comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol and optionally including not more than 10 mol% of negatively charged vesicle-forming lipids, which liposomes have a selected mean particle diameter in the size range between about 40 – 200 nm and contain a corticosteroid for the site-specific treatment of inflammatory disorders, characterised in that the corticosteroid is present in a water soluble form.

2. Composition according to claim 1, characterised in that the corticosteroid is selected from the group consisting of systemically administered corticosteroids.

3. Composition according to claim 2, characterised in that the systemically administered corticosteroids are selected from the group consisting of prednisolone, dexamethasone and methylprednisolone.

4. Composition according to claim 1, characterised in that the corticosteroid is selected from the group of topically applied corticosteroids.

5. Composition according to claim 4, characterised in that the topically applied corticosteroids are selected from the group consisting of budesonide, flunisolide and fluticasone propionate.

6. Use of a pharmaceutical composition, comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol and optionally including not more than 10 mole percent of negatively charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40 – 200 nm and containing a corticosteroid, for the preparation of a

medicament effective in the site-specific treatment of inflamed tissues or regions after parenteral administration, characterised in that the corticosteroid is used in the medicament in a water soluble form.

7. Use according to claim 6, characterised in that as the corticosteroid a systemically effective corticosteroid is used.

8. Use according to claim 6, characterised in that as the corticosteroid a topically effective corticosteroid is used in the medicament.

9. Use according to any one of claims 6 - 8 in the site-specific treatment of rheumatoid arthritis.

10. Use according to any one of claims 6 - 8 in the site-specific treatment of multiple sclerosis.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2002 (13.06.2002)

PCT

(10) International Publication Number
WO 02/045688 A3

(51) International Patent Classification[7]: A61K 9/127, 31/573

(21) International Application Number: PCT/EP01/14633

(22) International Filing Date: 7 December 2001 (07.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00204372.7 7 December 2000 (07.12.2000) EP

(71) Applicant *(for all designated States except US)*: YAMANOUCHI EUROPE B.V. [NL/NL]; Elisabethhof 19, NL-2353 EW Leiderdorp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: METSELAAR, Josbert, Maarten [NL/NL]; Dept. of Pharmaceutics, Faculty of Pharmacy, Utrecht Institute of Pharmaceutical Sciences, P.O. Box 80082, NL-3508 TB Utrecht (NL). WAUBEN, Marca, Henriette, Michaela [NL/NL]; Dept. of Immunology, Faculty of Veterinary Medicin, e, Institute of Infectious diseases and Immunology, P.O. Box 80165, NL-3508 TB Utrecht (NL). STORM, Gerrit [NL/NL]; Dept. of Pharmaceutics, Faculty of Pharmacy, Utrecht Institute of Pharmaceutical Sciences, P.O. Box 80082, NL-3508 TB Utrecht (NL).

(74) Common Representative: YAMANOUCHI EUROPE B.V.; Dept. legal Affairs Europe, P.O. Box 108, NL-2350 AC Leiderdorp (NL).

(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TT, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

(88) Date of publication of the international search report:
14 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/045688 A3.

(54) Title: COMPOSITION FOR TREATMENT OF INFLAMMATORY DISORDERS

(57) Abstract: A pharmaceutical composition for parenteral administration, comprising liposomes composed of non-charged vesicle-forming lipids, including up to 20 mole percent of an amphipathic vesicle-forming lipid derivatised with polyethyleneglycol, and optionally including not more than 10 mole percent of negatively charged vesicle-forming lipids, the liposomes having a selected mean particle diameter in the size range between about 40-200 nm and containing a water soluble corticosteroid for the site-specific treatment of inflammatory disorders, is provided.

INTERNATIONAL SEARCH REPORT

Interl Application No
PCT/EP 01/14633

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/127 A61K31/573

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 07466 A (LIPOSOME TECHNOLOGY INC) 14 April 1994 (1994-04-14) page 6, line 11 - line 30 page 7, line 6 - line 26 page 6, line 31 -page 7, line 2 page 36, line 17 - line 22 page 38, line 1 - line 28 example 12 claims 1,8 & EP 0 662 820 A 19 July 1995 (1995-07-19) cited in the application ---	1-10
X	EP 1 044 679 A (TERUMO CORP) 18 October 2000 (2000-10-18) paragraph '0017! - paragraph '0022! paragraph '0045! paragraph '0120! - paragraph '0123! paragraph '0182! --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2002	05/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

INTERNATIONAL SEARCH REPORT

Inter l Application No
PCT/EP 01/14633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 622 072 A (WAKAMOTO PHARMA CO LTD) 2 November 1994 (1994-11-02) examples 1,6-8,10,29 ---	1-10
A	GONZALEZ-ROTHI RICARDO J ET AL: "Pulmonary targeting of liposomal triamcinolone acetonide phosphate." PHARMACEUTICAL RESEARCH (NEW YORK), vol. 113, no. 11, 1996, pages 1699-1703, XP000998067 ISSN: 0724-8741 abstract -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No
PCT/EP 01/14633

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9407466	A	14-04-1994	US	5356633 A	18-10-1994
			AT	152614 T	15-05-1997
			AU	5323194 A	26-04-1994
			CA	2146565 A1	14-04-1994
			DE	69310527 D1	12-06-1997
			DE	69310527 T2	04-12-1997
			EP	0662820 A1	19-07-1995
			ES	2104184 T3	01-10-1997
			WO	9407466 A1	14-04-1994
EP 1044679	A	18-10-2000	EP	1044679 A1	18-10-2000
			WO	0025748 A1	11-05-2000
			JP	2001055343 A	27-02-2001
EP 0622072	A	02-11-1994	CA	2120197 A1	03-10-1994
			DE	69425773 D1	12-10-2000
			DE	69425773 T2	13-06-2001
			EP	0622072 A2	02-11-1994
			JP	6336442 A	06-12-1994
			US	5569464 A	29-10-1996